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The threshold for detecting a rise in airflow resistance during tidal breathing is lower in older patients with COPD than in healthy people of similar age

Abstract

Introduction: To investigate whether or not the threshold for subjectively detecting an increase in the resistance to airflow (LDT) during tidal breathing at rest rises in older age in patients with COPD, as it does in healthy people and asthmatics in remission. Material and methods: We conducted an open cross-sectional study of 31 older patients (age 55–89) with COPD and 60 healthy volunteers (age 55–86). Inspiratory and expiratory resistive load detection thresholds (ILDT and ELDT respectively) and spirometry were measured.

Results: The mean (SD) ILDT was 5.93 (7.02) kPa.s/L in COPD patients, compared to 11.11 (8.47) in healthy people ($P < 0.001$) in the same age range. There was no significant correlation between ILDT and age in the COPD group ($r = -0.182$, $P = 0.326$), though significant correlation with age was found in healthy people ($r = 0.591$, $P < 0.001$). ILDT and ELDT in COPD patients correlated significantly with the FEV1/FVC ratio ($r = 0.367$, $P = 0.048$ and $r = 0.481$, $P = 0.007$ respectively) but not with other spirometry indices, height, weight, BMI, oxygen saturation or smoking pack-years.

Conclusion: LDT during tidal breathing appears to be sensitized, and thereby lower, in older COPD patients, possibly due to altered central regulation of the threshold or as a consequence of the effect lung compliance, recoil and volume changes have on afferent input from mechano-receptors in COPD. Older COPD patients with good cognition are therefore likely to be as aware of changing airways resistance as younger patients and take appropriate therapeutic action.

Key words: airflow resistance sensing, ageing, spirometry, chronic obstructive pulmonary disease

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Introduction

In previous studies we showed that the threshold for the subjective detection of an increase in an incrementally applied external resistive load to airflow (LDT) during tidal breathing rises with age in a substantial proportion of healthy people and asthmatic patients in remission [1, 2]. We contended that this had implications for elderly patients who might consequently be less able to sense the early stages of a relapse in their asthma and therefore delay taking appropriate action. That argument was consistent with the commonplace clinical experience that older asthmatics tend to present later than younger patients when they are having an exacerbation. Following the same logic for the study reported in this paper we hypothesized that patients with chronic obstructive pulmonary disease (COPD) would be expected to exhibit a similar age effect unless the chronically high airflow resistance in patients with COPD results in an adaptive response leading to higher detection thresholds across the older (above 55 years) age range and thereby a loss of the progressive age-related rise seen in normal subjects and well-controlled asthmatics within the 55 to 80+ age band. This might in turn lead to a generally blunted sense of raised airflow resistance, one consequence of which could be a tendency to under-ventilate in response to rising resistance and could arguably contribute to carbon dioxide retention in some COPD patients

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[3]. There is some empirical evidence for this contention though almost all extant studies have been carried out in patients with COPD using sequential bronchoconstriction or under dynamic external airflow loading conditions [4–6]. During induced bronchoconstriction airflow resistance rises in relatively large and unpredictable increments so it is difficult to determine accurately the level of airways resistance at which a sensation of impaired airflow is first felt subjectively. Therefore, studies of that type might not provide the best insight into the influence of ageing and chronic airflow limitation on one of the most clinically relevant issues, namely whether the effect of age on airflow resistance sensing remains a factor in COPD, or is exaggerated, or is over-ridden by the neuro-physiological consequences of persistently high airflow resistance. Our method for measuring LDT was developed to address the limitations of the bronchoconstriction methods [1]. A full review of the mechanisms determining resistance sensing are outside the scope of this paper, though the background physiology and related hypotheses have been covered in depth in our previous publications [1, 2, 7]. In short, detecting subjectively an increase in airflow resistance is the result of sensing that a change has occurred in the relation between inspiratory effort and the resulting tidal volume, an example of length-tension sensing [8–10]. The dynamic central monitoring of such breath-by-breath lung volume movements must depend on sensory information arising in thoracic mechano-receptors, including those located in the diaphragm, chest wall, airways and lung parenchyma. The deterioration of proprioceptive acuity with age has been well documented for a number of functions such as postural sway, gaze stability and point relocation [11–16]. If an analogous change occurs in the accuracy and central processing of afferent mechano-receptor traffic from the diaphragm and chest wall it can be hypothesized that the resting LDT would rise progressively with age in patients above 55 years (the range within which most diagnosed COPD patients reside) and become more variable, as was observed in healthy people and asthmatics in remission [1, 2]. This was the primary hypothesis to be tested by the study presented in this paper. Therefore, we conducted an experiment to explore LDT in patients with COPD in relation to age and a number of other variables of relevance in COPD including spirometric indices and smoking exposure.

Material and methods

Study design and subject selection

We conducted a prospective open cross-sectional study. Patients with a diagnosis of COPD confirmed by pulmonologists using nationally agreed criteria [17] were invited to consent to participate. Potential participants were selected from a departmental diagnostic list. A preliminary powers calculation for comparing LDT between groups, based on a pilot study, indicated that from the 150 potential participants available for the study, and assuming a population proportion of 50% and margin of error of 20%, a sample of 30 would be the minimum for showing significant difference with 95% confidence. The selection was quasi-random as all patients with COPD on the list were initially considered before application of the inclusion and exclusion criteria and all those who accepted the invitation to participate entered the study. The inclusion criteria were: adults with a diagnosis of COPD, at least 6 weeks since any exacerbation requiring an intervention and currently back to clinical baseline, abbreviated mental test (AMT) [18] above 7, willing to consent to take part in the study. The exclusion criteria were: contra-indications to performing spirometry (such as recent eye surgery), history of significant cognitive impairment or overt dementia (unlikely to be able to perform the tests) [19], currently taking any medication that can alter respiratory sensory function or cause sedation (such as opioids or benzodiazepines), any known or apparent central or peripheral nervous system condition that might alter respiratory sensory function (such as stroke or sensory neuropathy), pulmonary co-morbidities that could alter the LDT (such as pulmonary fibrosis).

We also harvested LDT data from a study of normal people [1] to provide a comparison group across the same age range as the COPD study group and with approximately the same distribution of ages over the range. This was done after the COPD group had been recruited to enable the age range to be comparable. The normal group were all lifelong non-smokers, or ex-trivial smokers (< 1 pack-year), and all had normal spirometry indices and no history of respiratory disease or any other condition or medication that might alter their LDT measurements. They were all either university employees or staff and volunteers at our base hospital.

Measuring the LDT

We used exactly the same apparatus as in our previous studies of healthy people and asthmatic patients [1, 2], constructed with standard respiratory physiology equipment (Harvard Apparatus®). It was comprised of a flanged rubber mouthpiece connected to a unidirectional low resistance valve that was attached by a push-fit connector to an airflow resistor by a 90 cm section of low resistance respiratory tubing. The resistor could therefore be applied in either the inspiratory or expiratory mode. A disposable microbiological filter (Vitalograph®) was inserted between the mouthpiece and valve. The dead space was less than 50 ml and did not vary. In preparatory experiments [1] it was found that a resistor aperture of lentiform cross-sectional shape provided the most consistent and near-linear calibration curve over the flow range anticipated during tidal breathing. Calibration of the resistor through its operational range was carried out with the resistor incorporated in the apparatus and using pumped air at 5 litres per minute at room temperature (20–24 degrees centigrade) and ambient humidity, with flow determined by a bobbin flow meter (Rotameter®) and pressure by a water manometer using standard laboratory methods. In our previously published studies on volunteers willing to perform repeated LDT measurements we found a mean coefficient of variation of 4.3% in people under 65 years of age and 6.2% in those over 64 years of age (5 subjects performed 20 consecutive inspiratory LDT measurements in each group). We also found no significant differences between the LDT values of men and women when compared within young, middle aged and elderly age groups [1].

A detailed description of the LDT measurement procedure we developed has been published elsewhere [1, 2] and it is recommended that researchers wishing to construct a similar apparatus and to apply the technique should refer to those papers. In summary, LDT measurements were made in a quiet room with sources of distraction minimised. The patient was seated and requested to breathe tidally through the LDT apparatus wearing a nose clip and a pulse oximetry finger probe (Suaok® FS 10D). After a settling period of about 1 minute the resistor was closed, silently and out of sight, in half millimetre long-axis increments every 2 or 3 breath cycles until the subject indicated by raising a hand that they had reached the point at which they could first feel definite resistance to breathing. The aperture setting was recorded and later compared with the calibration curve to determine the measurement. Three such measurements were made in each of the inspiratory and expiratory modes. The means of the 3 readings were taken as the recorded inspiratory and expiratory LDTs (ILDT and ELDT respectively). No readings were discarded. Corrections for actual temperature, humidity and atmospheric pressure were not made on individual study days because they were found to be too small to be of significance.

Spirometry

Spirometry was performed on each participant using a desktop spirometer (NDD EasyOn-PC®). The ERS/ATS performance and interpretation standards [16] for forced spirometry were applied and recordings were made of peak expiratory flow rate (PEF), forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC). Subjects unable to have these indices measured to the required standard were not included in the data analysis. Height, weight, sex and age were recorded and used to calculate predicted values electronically using regional tables for Caucasians.

Study sequence

The order of data collection for each subject was: invitation and information, consent, AMT score, Medical Research Council Dyspnoea Scale (MRCDS) [20](used with permission of the Medical Research Council), record current medication, record clinical data (smoking history, sputum production and timing of last exacerbation), check inclusion and exclusion criteria, spirometry, LDT measurement.

Statistical testing

Some continuous data were found to be approximately normally distributed on visual assessment, though this was not clear in all cases and the Shapiro Wilk test rendered values of < 0.05 in every case. Because of the uncertain distribution and small samples, groups were compared by the Mann Whitney U test. To take account of some outlying LDT data points in the relatively small samples correlation coefficients were calculated by the Spearman method, with the Bonferroni correction for multiple testing. For categorical data Fisher's exact test was used to allow for the relatively small sample size. A significance level of 5% was adopted for group comparisons and correlations. All calculations were conducted using online software (socscistatistics.com).

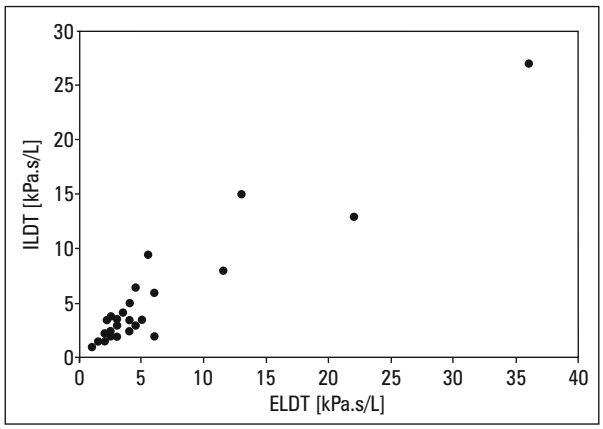

Figure 1. Correlation of ILDT with ELDT for COPD patients (N = 31, r = 0.959, P > 0.001, Spearman method). The line of identity between the axes is shown. ILDT — inspiratory airflow resistance load detection threshold; ELDT — expiratory airflow resistance load detection threshold

Results

We studied 31 COPD patients (25 men, all Caucasian) with a mean age of 72 years (median 77, range 55–89). All were smokers or ex-smokers with a mean exposure of 46 pack-years (range 15–94). They were all clinically stable and at their usual baseline at the time of the study. Their regular medication consisted of combined long-acting anti-muscarinic agent (LAMA), long-acting beta-adrenergic agonist (LABA) and corticosteroid (CS) by inhaler in 18 patients, LAMA plus LABA by inhaler in 3, CS plus either LAMA or LABA by inhaler in 6, LAMA alone by inhaler in 3 and no medication in 1. The mean AMTS was 9.5 (range 8–10), MRCDS was 2.7 (range 1–5), FEV_1 46% of predicted (range 23–59) and FEV1/FVC ratio 47.3% (range 25.5–68.3). It was confirmed that all met the spirometry criteria for COPD [17]. The mean oxygen saturation at rest breathing air was of 95% (range 88–97) and none had a fall in oxygen saturation when having their LDTs measured. Their mean body mass index (BMI) was 26 kg/m^2 (range 18.5–37.8).

The mean (SD) ILDT and ELDT values were 5.93 (7.02) kPa.s/L (range 1.5–36) and 5.19 (5.20) kPa.s/L (range 1–27) respectively, with no significant difference. Though the between-subject range was large there was close within-subject numerical concordance when comparing both indices (Figure 1) with a high degree of correlation (r = 0.959, p < 0.001) and the line of regression through the points was close to the line of identity between the axes, indicating an absence of tidal phase bias. Correlations between ILDT, ELDT and other variables are shown in Table 1. There was no significant correlation between ILDT and age (Figure 2), FEV_1, FVC, PEF, height, BMI, oxygen saturation and smoking pack-years. However, there was significant correlation between ILDT and FEV_1/FVC and between ELDT and FEV_1/FVC. No significant correlations with ILDT or ELDT emerged when FEV_1, FVC and PEF were expressed as percentages of the predicted values derived from age, height, BMI and sex. The mean (SD) ILDT of patients who produced sputum on most days (N = 18) was 5.64 (5.14) kPa.s/L and that of those

Table 1. Coefficients of correlation (r) and probability values (P) for ILDT and ELDT compared with a number of variables. (Spearman method, N=31).

	R	P	R	P
Age	-0.182	0.326	-0.164	0.377
FEV_1	0.072	0.710	0.088	0.690
FVC	0.154	0.410	0.161	0.440
PEF	0.004	0.989	0.008	0.991
FEV_1/FVC	0.367	0.048*	0.481	0.007*
Height	-0.322	0.130	-0.299	0.111
Weight	0.200	0.301	0.223	0.341
BMI	-0.099	0.616	-0.104	0.625
Oxygen saturation	0.232	0.294	0.244	0.317
Smoking pack-years	0.019	0.966	0.023	0.974

BMI — body mass index; ; ELDT — expiratory airflow resistance load detection threshold; FEV1 — forced expiratory volume in 1 second; FVC — forced vital capacity; ILDT — inspiratory airflow resistance load detection threshold; PEF — peak expiratory flow rate

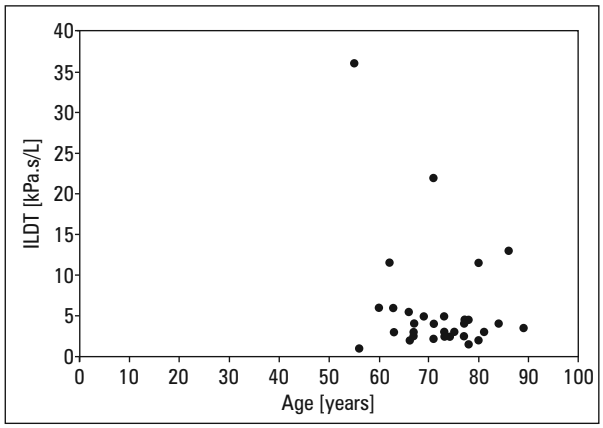

Figure 2. No significant correlation was found between ILDT and age in COPD patients (N = 31, r = -0.182, P = 0.326, Spearman method). ILDT — inspiratory airflow resistance load detection threshold

who produced sputum occasionally or never (N = 13) was 6.51 (9.32) kPa.s/L and there was no significant difference (p = 0.781) .

In the healthy comparison group (N = 60, 25 men, all Caucasian), the mean age was 70 years (median 74, range 55–86). The mean FEV_1 was 98% of predicted (range 86–117) and the mean FEV_1/FVC ratio was 77% (range 72 – 81) and was between 94 – 112% of predicted and thereby within the normal range for men and women. Their mean BMI was 27.0 kg/m^2 (range 21.0–36.5), all had an AMT score of 10 and MRCDS score of 0. There were no significant differences in the ages or BMIs of the COPD and healthy groups (P = 0.253 and P = 0.304 respectively), though there was a significantly higher proportion of women in the healthy group (P = 0.05). The mean (SD) ILDT was 11.11 (8.47) kPa.s/L which was significantly higher than in the COPD group (P = 0.005). In the healthy subjects a significant positive correlation was found between ILDT and age across the comparison age range (r = 0.589, P < 0.001)

The findings for ELDT were very similar for all comparisons.

Discussion

The findings of the study did not confirm the hypothesis we set out to test. On the contrary, we found that the mean LDTs in patients with COPD were lower rather than higher than those of the older healthy comparison group within the same age range in this study and very similar to the young and middle-aged healthy subjects in our previous study [1]. Further, there was no apparent tendency for LDTs to rise with age in the COPD group, unlike healthy control patients, across the 55 to 85 age range. There must be some caution in drawing any firm conclusions from these data, particularly the correlative relationships, because the sample was relatively small and the levels of statistical significance, or lack thereof, must be interpreted in the light of that limitation. Nevertheless, in group comparisons the clearly significantly lower mean LDT values in COPD patients compared to healthy people in the same age range is noteworthy. It appears that that the physiological burden of chronically raised airways resistance does not have a blunting or down-regulatory effect on the ability to detect subjectively a rise in airflow resistance in COPD. Indeed, there appears to be preservation of that ability across an older age range in COPD in contrast to healthy people and asthmatics in remission [1, 2]. The reasons for this observation are not clear. It is known that people with COPD breathe with an exaggerated intrathoracic pressure swing between inspiration and expiration and at a higher and less mechanically advantageous lung volume [21] so it can be postulated that they could be predisposed to finer detection of perturbations in length-tension cycles during tidal breathing and thereby conserve LDT detection sensitivity into old age. If that were a contributary mechanism it might be expected that LDTs would rise in line with the FEV1/FVC ratio as those with higher ratios can arguably be considered to have less impairment of respiratory mechanics. We found such a rise that was of borderline statistical significance for ILDT though more clearly significant for ELDT. This supports the rationale described, though the number of participants was probably too low to comment on that aspect with certainty. Further, the unexpected negative correlation we found between LDTs and age might also be due to the deterioration in lung and chest wall mechanics over time in people with COPD, which might consequently eclipse the effects of ageing that we found in healthy subjects in this study and in previous work [1, 2]. Again, the small sample size, which was probably insufficiently powered for that particular part of the analysis precludes a firm conclusion. However, the trend makes physiological sense and needs to the specific focus of another study. The age and BMI characteristics of the groups were comparable so it is unlikely that those variables could account for the differences we observed. There was a significantly larger proportion of women in the healthy group. However, in our previous work [1, 2] we found no differences in the pattern of the relationship between ILDT and age between men and women, and that also appeared to be the case on scrutiny of the distribution of measurements in this study, though the samples were too small for confident statistical analysis.

In healthy people and patients with COPD the detection thresholds were below the resistance levels that we found to be distressing or uncomfortable in young and middle-aged healthy subjects who took part in our preliminary resistance ranging studies [1]. However, it is not known whether the afferent input from chest wall and diaphragmatic mechano-receptors has a linear influence on central length-tension processing. If not, it can be argued that the small additional resistances used when testing for LDT would have a proportionally larger central effect for COPD patients already tidally breathing at higher

lung volumes against chronically raised airflow resistance and greater recoil forces, thus allowing an alternative explanation for our observations to be posited. There is not complete agreement as to whether external airflow resistance loading is a valid analogue for intrinsic airways resistance, though it has been acknowledged that mechano-receptors must be involved [22]. The role of afferent sensory traffic from airway and lung parenchymal receptors [23] does not appear to be dominant in normal subjects, though could be more contributary to determining the sensitivity of central length-tension processing in those with lung disease, including COPD [24]. However, it has been observed that lung transplant patients, who have denervated lungs but intact chest wall and diaphragmatic sensation, retain the ability to judge lung volumes and have normal sensitivity to changes in external airflow resistance [25–27], which reinforces the key role of the mechano-receptors in the skeleto-muscular structures in airflow resistance sensing. The findings of our previous studies of healthy people and well-controlled asthmatics suggested that an age-related reduction in the sensitivity of airflow resistance sensing could be at least partly responsible for the clinically observed reduction in the ability of elderly people to detect early the changes in airflow resistance that occur, for example, in a worsening of asthma. However, the same does not seem to be the case for patients with COPD who appear to retain an acuity of airflow resistance sensing that is more typical of young adults.

There are clinical implications to the findings of this study. Our findings suggest that patients with COPD who are not undergoing an exacerbation are likely to be able to detect a rise in their airway resistance with a high degree of acuity at any age. Therefore, the concern that elderly COPD patients might delay taking reliever inhaled broncho-dilator therapy, or present later to medical services for help during an exacerbation due to ageing effects on resistance sensing is refuted, unlike some elderly asthmatics. It is apparently therefore not necessary to advocate that the COPD treatment guidelines [17] need take account of age for that specific reason. Of course, elderly patients with COPD do have a higher prevalence of other factors that complicate their management, such as dementia and heart failure, which must be acknowledged in their treatment plans.

Conflict of interest

None of the authors has any conflict of interest to declare.

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